Expert Opinion

Rimonabant: a selective blocker of the cannabinoid CB1 receptors for the management of obesity, smoking cessation and cardiometabolic risk factors

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Rimonabant is the first selective blocker of the cannabinoid CB1 receptors being developed for the treatment of obesity, tobacco smoking and cardiometabolic risk factors. Following 1 year of treatment, rimonabant 20 mg/day leads to greater weight loss compared with placebo. Therapy with rimonabant is also associated with favourable changes in serum lipids and an improvement in glycaemic control in Type 2 diabetics. At the same dose, rimonabant significantly increases the cigarette smoking quit rates compared with placebo. Rimonabant appears to be generally well tolerated, with primary side effects of mild nausea, diarrhoea, anxiety and depression. As an agent with a novel mechanism of action, rimonabant has the potential to be a useful adjunct to lifestyle modification in the treatment of obesity, metabolic syndrome and cigarette smoking.

1. Metabolic syndrome

Systematic and thorough public health measures and sophisticated advances in medical interventions have led to a steady increase in life expectancy in the developed world in the last century; however, recent projections forecast a decline in life expectancy in the 21st century [1]. Cardiovascular disease will remain the leading cause of morbidity and mortality in the developed world but the reports warn of a catastrophic effect of the global obesity epidemic on rates of diabetes mellitus and cardiovascular disease in the upcoming years. Currently, 28% of men and 34% of women are obese in the US. These rates are rising, and the largest increase has affected children, minorities, and those in the lower socioeconomic strata [2].

On the surface, clinicians have long noted the adverse effects of obesity on cardiovascular health, and have observed higher rates of Type 2 diabetes in obese patients. In a recent case-control study involving > 27,000 subjects, Yusuf *et al.* [3] demonstrated a strong, graded correlation between a higher waist:hip ratio and an increased risk of myocardial infarction [3]. Fittingly, the old view of adipose tissue as an inert storage depot was supplanted recently by its depiction as a complex and dynamic endocrine organ. It is directly involved in the regulation of food intake, and secretes hormones that influence both appetite and the motivation to eat. Adipose tissue synthesises and secretes a variety of factors (adipokines) that contribute to insulin resistance, vascular endothelial dysfunction, atherogenesis and inflammation [4,5]. Thus, obesity is not an isolated pathophysiological entity, but part of a constellation of risk factors, where it frequently coexists with hypertension, glucose intolerance and dyslipidaemia. In 2001, NCEP-ATP (National Cholesterol Education

Programme Adult Treatment Panel) III put forth specific guidelines that define a population with 'metabolic syndrome' (**Box 1**; **Table 1**) [6]. Individuals who are diagnosed with metabolic syndrome are at a high risk of developing diabetes and clinically significant atherosclerosis. The presence of metabolic syndrome is associated with a significant increase in the risk of myocardial infarction, stroke, and overall cardiovascular mortality [7].

Cigarette smoking is another important modifiable risk factor for atherosclerosis, and increases an individual's risk of coronary atherosclerosis and sudden death by two- to fourfold [8]. Mortality from cardiac events can be predicted from the number of cigarettes smoked/day, duration of the smoking habit and depth of smoking inhalation [8]. Rates of smoking in the US have declined appreciably since peaking in the 1960s; however, > 20% adults smoke routinely [9] and global cigarette consumption is on the rise.

2. Current therapies for obesity and tobacco smoking

Decrease in body weight is associated with favourable changes in the lipid profile and C-reactive protein (CRP), improved glycemic control and a decrease in mortality [10,11]; however, success with behaviour modification and currently available medications in achieving and sustaining even mild weight loss is limited.

Currently available pharmacotherapy for obesity includes: phentermine, which promotes satiety; sibutramine (an anorexigen), which acts by inhibiting re-uptake of noradrenaline and 5-HT; and orlistat, which alters fat absorption. Phentermine and sibutramine mimic the actions of noradrenaline and affect weight loss by causing early satiety. Cardiovascular adverse effects, such as hypertension and tachycardia, limit their use, especially in patients with cardiac comorbidities. Use of orlistat is limited by a frequent occurrence of bothersome gastrointestinal side effects, as well as limited efficacy in producing sustained weight loss.

Surgical procedures, such as gastric banding or gastric bypass, are effective for sustained weight loss, but are clearly invasive and associated with a significant rate of complications [12]. Therefore, these procedures are generally used for patients with morbid obesity (body–mass index [BMI] > 40 kg/m²) and those with obesity-related complications [13].

Smoking cessation is associated with a rapid decrease in the risk of developing adverse cardiovascular events, including myocardial infarction, stroke and sudden death [14,15]. Treatment for tobacco smoking typically involves a combination of behavioural and pharmacological therapy [16]. Pharmacological therapy consists of nicotine replacement and buproprion. Nicotine replacement is available in transdermal, intranasal and buccal forms, and increases the odds of quitting smoking by ~ 1.5- – 2-fold [17]. Buproprion is an antidepressant that is approved in an extended-release form as an adjunct in smoking cessation. In a 7-week, placebo-controlled trial, buproprion was associated with higher quit rates than placebo [18]. Nevertheless, most of the subjects who quit smoking were smoking tobacco again following 1 year of follow up, which is consistent with most clinicians' clinical experience. Unfortunately, smoking cessation is also frequently associated with weight gain, which is considerable in some patients, and may serve as an additional barrier for those who are considering tobacco quiting [19].

In summary, results for the treatment of obesity and smoking have generally been disappointing to date. Nevertheless, a reduction in modifiable risk factors for atherosclerosis and coronary events is an essential component of primary and secondary prevention of heart disease (**Box 2**) [20,21]. Manipulation of the endocannabinoid system via blockade of cannabinoid (CB1) receptors with rimonabant is an intriguing new approach that addresses obesity, and metabolic and smoking manipulation of the endogenous cannabinoid system, metabolic syndrome and smoking.

3. The endocannabinoid system

Cannabis sativa (hemp) has been used for millennia as a source of fibre and oil, and as a source of recreational drugs (marijuana and hashish). The plant contains > 60 alkaloids, the primary one being Δ^9-tetrahydrocannabinol (THC). In addition to its psychoactive effects [22], THC administration to normal subjects results in tachycardia, mild hypertension, dry mouth and increased appetite. Synthetic THC (dronabinol) is used to treat postchemotherapy emesis, as well as anorexia, associated with the HIV infection.

3.1 Cannabinoid receptors

THC and other exogenous cannabinoids interact with specific G-protein-coupled receptors: CB1 and -2, which were described in the late 1980s and cloned recently [23,24]. The CB1 receptors are overwhelmingly distributed in the brain [25] and adipose tissue [26], but are also found in the myocardium [27], vascular endothelium [28], liver, muscle and sympathetic nerve terminals [29]. The CB2 receptors are primarily located in the lymphoid tissue and peripheral macrophages but also in the brain [30,31]. There are recent reports of a possible additional cannabinoid receptor, tentatively named CB3 [32].

Cannabinoid receptors have affinity for at least two endogenous ligands: small lipid molecules such as arachidonylethanolamide (anandamide); and 2-arachidonoyl glycerol (2-AG). In the nervous system, endocannabinoids act by retrograde activation of the presynaptic cannabinoid receptors (**Figure 1**) [33]. Postsynaptic depolarisation results in the opening of the Ca^{2+} channels and activation of synthetic enzymes, which generate endocannabinoids. Alternatively, activation of postsynaptic metabolic glutamate receptors may activate phospholipase C, and generate 2-AG through an intermediate product (diacylglycerol). Following their synthesis, endocannabinoids rapidly leave the postsynaptic cell terminal

Box 1. Components of metabolic syndrome.
At least three of the following traits: Abdominal obesity • Men > 102 cm (40 in) • Women > 88 cm (35 in) Serum triglycerides 150 mg/dl (1.7 mmol/l) Serum high-density lipoprotein cholesterol < 40 mg/dl (1 mmol/l) in men and < 50 mg/dl (1.3 mmol/l) in women Blood pressure > 130/85 mmHg Fasting plasma glucose 110 mg/dl (6.1 mmol/l)

Table 1. The effects of CB1 blockade on metabolic syndrome.

Central blockade (hypothalamus)	Decreased food intake
Peripheral blockade (adipose tissue)	Decreased abdominal fat (waist circumference) ↑ Adiponectin ↑ Triglycerides ↑ High-density lipoprotein ↑ Small dense low-density lipoprotein ↑ C-reactive protein ↑ Insulin resistance

and activate CB1 receptors on the presynaptic membranes. A change in the conformation of the receptor-coupled G protein directly inhibits presynaptic Ca^{2+} influx channels, and thus decreases the release of a neurotransmitter vesicle [33]. Endocannabinoids are then rapidly inactivated via cellular uptake and enzymatic hydrolysis [34].

4. Physiology of the cannabinoid system

4.1 Cardiovascular effects

In normal animal models, acute administration of an endocannabinoid produces a characteristic triphasic haemodynamic response: a brief, vagally mediated bradycardia and hypotension; an equally brief pressor response; and a dominant, more prolonged vasodepressor response [35]. Most of the prolonged vasodepressor effect occurs secondary to the suppression of the sympathetic outflow and is CB1-mediated [36]. It is probable that endocannabinoids also affect the blood vessels directly, where they induce vasodilation both via CB1 receptors [37] and through the endothelium-dependent increase in nitric oxide synthesis [38].

In animal models of hepatic disease, endocannabinoids have been shown to mediate the vasodilatory state through their interaction with CB1 receptors [39]. Finally, experiments show that some states of extreme haemodynamic distress may be propagated by endocannabinoids; for example, under conditions of haemorrhagic [40], cardiogenic [41] or septic shock [42,43], macrophages and circulating platelets elaborate anandamide, which contributes to the persistence of hypotension and organ hypoperfusion.

4.2 Metabolic effects

Cannabinoid receptors and ligands are present in high concentrations in all of the tissues that play an important role in the regulation of food intake, namely: adipose tissue; the limbic system; and hypothalamus. Overwhelming evidence now supports the notion that endocannabinoids are central to the regulation of metabolism and body composition. They maintain this balance by enhancing central orexigenic drive and increasing peripheral lipogenesis [44]. Administration of CB1 agonists induces hyperphagia in rodents [45-47] and antagonism of CB1 receptors prevents compensatory

overeating during forced starvation in rats [48]. On the other hand, administration of leptin suppresses endocannabinoid synthesis [48]. Likewise, mice lacking CB1 receptors exhibit a lean phenotype despite being fed a high-fat, obesity-promoting diet, primarily as a result of spontaneously-reduced caloric intake [44,49].

4.3 Other effects

Endocannabinoids are also thought to be central in addiction and relapse behaviours by modulating cue reactivity and conditioned reinforcement following prolonged abstinence of drug and natural reinforcers [50]. This has been demonstrated in models of cocaine [51], heroin [52], amphetamines [53] and alcohol [54] addiction.

Studies on the role of cannabinoids in nicotine addition have been particularly interesting. They show that the rewarding effects of nicotine can be effectively abolished in knockout mice lacking CB1 receptors [55], and that the administration of selective CB1 antagonists markedly diminishes nicotine-seeking behaviours [56].

5. Rimonabant

Rimonabant (SR-141716A; 5-[4-chlorophenyl]-1-(2,4-dichlorophenyl)-4-methyl-N-[piperidin-1-yl]-1H-pyrazole-3-carboxamide) was synthesised and described in 1994 by Rinaldi-Carmona et al. (**Figure** 2) [57]. The primary mode of action of rimonabant is antagonism at the CB1 receptors, although there is some evidence that at low concentrations it may act as an inverse agonist [58]. At very high concentrations, rimonabant also behaves as a CB2-receptor antagonist [57], blocks calcium and potassium channels [59], and may directly affect cellular gap junctions [60]. Pharmacokinetics of rimonabant have been comprehensively reviewed recently by Boyd and Fremming [61]. Additional reports indicate that rimonabant has no effect on the pharmacokinetics of warfarin, midazolam and oral contraceptives [62-64].

5.1 Background research in animal models

Work in rodent models demonstrated that rimonabant was associated with a reduction in food intake and an average 4% absolute loss of body weight in wild-type mice [48]. Knockout

Box 2. ACC/AHA unstable angina and non-ST elevation myocardial infarction guidelines: risk factor modification.

Smoking cessation
Achievement of optimal body weight
Daily exercise
AHA diet
Control of hypertension to blood pressure < 130/85 mmHg
Tight control of hyperglycaemia in diabetics
Lipid-lowering agents for LDL > 130 mg/dl
Lipid-lowering agent in LDL > 100 mg/dl after diet
Drug therapy if high-density lipoprotein < 40 mg/dl

Modified from ACC/AHA Guidelines for the Perioperative Cardiovascular Evaluation for Noncardiac Surgery. *J. Am. Coll. Cardiol.* (1996) **27**:910-948 [21]. © 1996 The American College of Cardiology Foundation and American Heart Association, Inc. Permission granted for one time use. Further reproduction is not permitted without permission of the ACC/AHA.
ACC: American College of Cardiology; AHA: American Heart Association; LDL: Low-density lipoprotein.

mice, deficient in the CB1 receptor, demonstrated no weight loss in the study, thus suggesting a specific CB1-mediated mechanism of weight loss. Initially, rimonabant decreases appetite but these effects are transient. During continued therapy, hyperphagia ensues, yet weight loss continues [63]. Most of the weight loss is accounted for by a marked 50% depletion in fat stores. Animals treated with rimonabant exhibit lower plasma glucose and insulin levels, as well as improved insulin resistance [66]. Notable recent findings by the same group [66] suggested that decreased food intake alone cannot account for the sustained weight loss during rimonabant treatment.

Microscopic evaluation of the adipose tissue from animals treated with rimonabant show adipocytes that are smaller than those in the control animals, and an overall appearance of the tissue reflects a decrease in cellular fat stores, rather than apoptosis of the individual adipocytes [63]. Strong support to the primary CB1 involvement in the effects of rimonabant is lent by DNA chip analysis, which shows that rimonabant induces gene modulations concordant with those seen in CB1 knockout animals [63], including an upregulation of several glycolytic enzymes, potentially explaining the glucose-lowering effect of rimonabant [63]. Expression of multiple genes coding for pro-inflammatory proteins, such as lipocortin, lysozyme M, plasminogen activator inhibitor-1 and lipopolysaccharide (LPS)-binding protein, ae downregulated [63].

5.2 Efficacy in obesity and metabolic syndrome

A total of four randomised trials were initiated under the aegis of the RIO (Rimonabant in Obesity) programme, sponsored by the drug's developer, Sanofi-Aventis (**Table 2**).
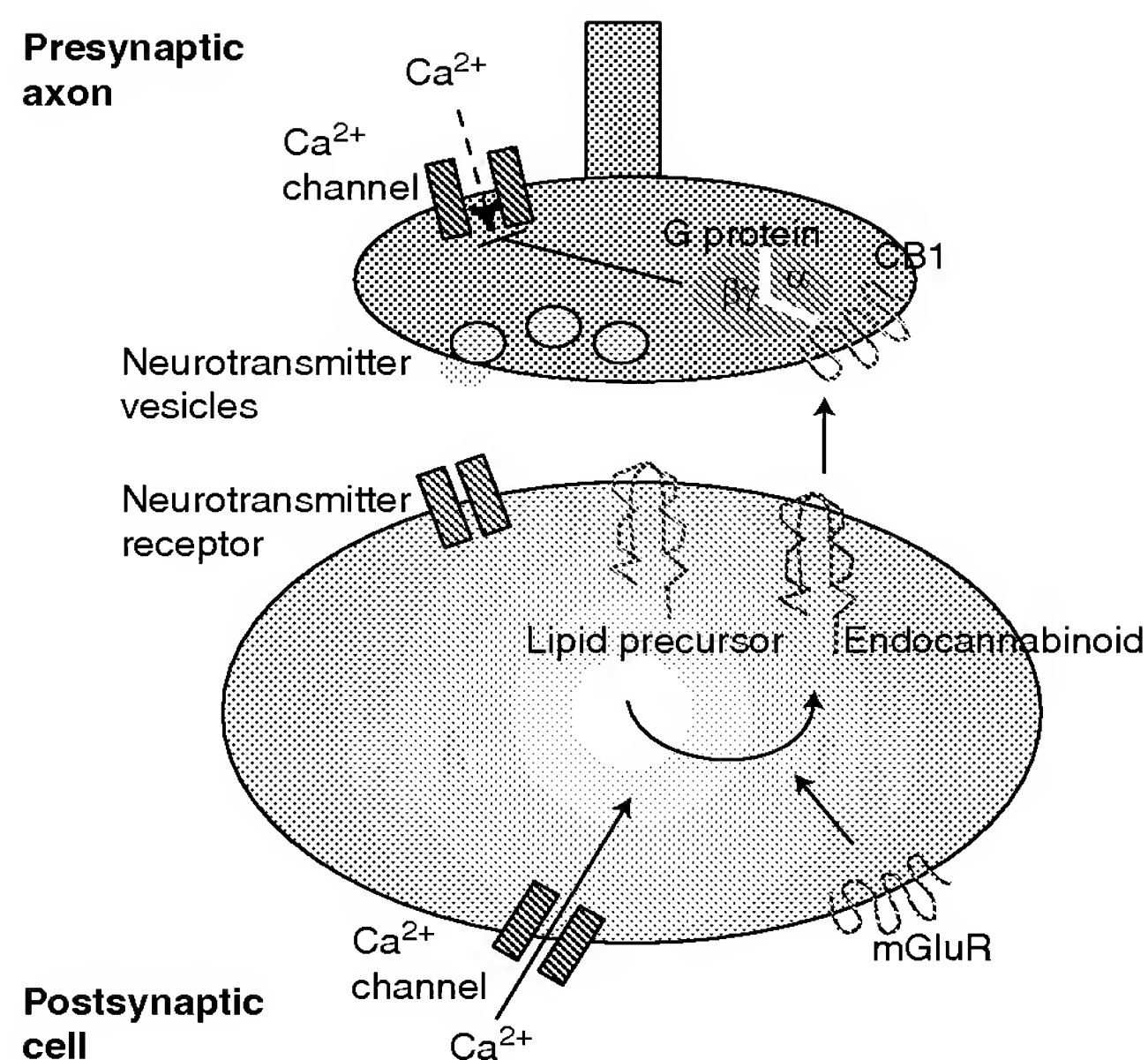

Figure 1. Retrograde signalling by endocannabinoids.
Reprinted with permission from WILSON RI, NICOLL RA: Endocannabinoid signaling in the brain. *Science* (2002) **296**(5568):678-682 [33]. © 2002 AAAS.
mGluR: Metabolic glutamate receptor.

All four studies were double-blind, placebo-controlled, parallel trials that randomly assigned its subjects to receive rimonabant 20 or 5 mg/day, or matching placebo. All of the RIO trials required their subjects to adhere to a hypocaloric diet and included regular consultations with a dietitian. The trials primarily differed in the inclusion criteria and follow-up periods.

In the RIO-Lipids trial, after a 4-week placebo run-in period, obese patients with untreated hyperlipidaemia were randomised to rimonabant or placebo, and followed for 1 year [67]. At the end of 1 year, patients in the rimonabant group lost significantly more weight than those in the placebo group. With rimonabant 20 mg/day, 33% of the patients lost ≥ 10% of their initial body weight compared with 7% of the patients on placebo. Therapy with rimonabant compared with placebo was also associated with a significant decrease in the proportion of patients meeting the criteria for metabolic syndrome (25.8 versus 41%, respectively). Consistent with the earlier animal data, the degree of inflammation (reflected by CRP levels) decreased significantly among patients in the rimonabant group [67].

Concurrently with RIO-Lipids, a similarly sized RIO-Europe trial [68,69] enrolled obese subjects with either hypertension or hyperlipidaemia. Patients were advised to follow a hypocaloric diet and were randomised to rimonabant 20 or 5 mg, or placebo. The study included a 4-week run-in period, similar to RIO-Lipids. The on-treatment analysis of
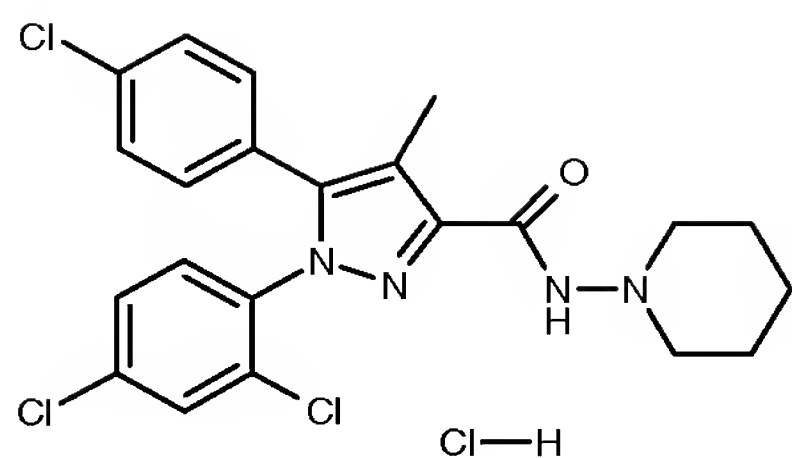
Figure 2. Chemical structure of rimonabant.

its results showed that following a full year of therapy, treatment with either rimonabant 5 or 20 mg/day was associated with significantly greater waist circumference reduction than placebo (6.5 cm for 20 mg, 3.9 cm for 5 mg and 2.4 cm for placebo). There were favourable changes in the lipid profile of subjects in both rimonabant groups: triglyceride levels decreased and high-density lipoprotein (HDL) levels increased, which may have been mediated by increased levels of adiponectin. The 2-year results from RIO-Europe were recently presented and demonstrate a substantial decrease in the proportion of subjects with metabolic syndrome with the combination of a hypocaloric diet and rimonabant 20 mg/day: 42.2% at baseline, 19.6% at 1 year [68] and 21.5% at 2 years [69].

The RIO-NA (North American) trial [70] used similar enrolment criteria to the other RIO trials but randomised its subjects to another year of therapy or matching placebo following 1 year of treatment with rimonabant or placebo. Although the 1-year outcomes were similar to the other RIO trials (**Figure 3**), subjects who completed only 1 year of rimonabant treatment and were then randomised to placebo had regained much of the lost weight during the period off the drug. Average weight loss for patients on rimonabant for the full 2 years, placebo for 2 years, or rimonabant for 1 year followed by placebo was 7.4, 2.3 and 3.2 kg, respectively. Consistent with the other RIO trials, rimonabant 20 mg/day was associated with an increase in HDL of 25%.

The latest component of the RIO programme was the RIO-Diabetes trial [71], which examined the effects of rimonabant on glucose control in obese subjects with Type 2 diabetes mellitus with an average baseline glycosylated haemoglobin [HbA_{1c}] of 7.3%. Standard oral hypoglycaemic regimen was continued throughout the study. At the end of 1 year of therapy, subjects in the high-dose rimonabant group lost significantly more weight than those in the placebo group (5.3 versus 1.5 kg, respectively). Average HbA_{1c} levels decreased by 0.6% in the high-dose rimonabant group, but increased in the placebo group by 0.1%. By the end of the study, 43% of all of the subjects treated with rimonabant were

able to achieve an optimal HbA_{1c} level of < 6.5% compared with just 21% of those receiving placebo.

5.3 Efficacy in smoking cessation

The role of rimonabant as a potential adjunct in smoking cessation is currently being examined in the STRATUS (Studies with Rimonabant And Tobacco Use) series of trials. All of the components of STRATUS are randomised, double-blind, placebo-controlled clinical trials, where subjects are randomised to rimonabant 20 (high dose) or 5 mg/day (low dose), or matching placebo.

In the first completed trial, STRATUS-US [72], subjects who smoked an average of 23 cigarettes/day were randomly assigned to receive rimonabant or placebo for 10 weeks, and were asked to quit smoking on day 15 of the study. Tobacco abstinence rates and body weight were assessed after 1 year. At the end of the study, only high-dose rimonabant resulted in a significantly higher abstinence rate than placebo (36 versus 21%). As expected from clinical experience, among subjects with prolonged abstinence, those in the placebo group gained weight (an average of 3.7 kg). However, those on rimonabant 20 mg/day only gained 0.6 kg.

Publication of the results from STRATUS-EU and STRATUS-WW (worldwide) is expected next year. The latter trial is examining the 'relapse rates' by following its subjects for ≤ 1 year after cessation of treatment.

5.4 Ongoing studies for other indications

Therapy with rimonabant induces significant, favourable changes in an individual's cardiometabolic risk profile as evidenced by weight loss, higher serum HDL, lower triglyceride levels and improved glycaemic control. However, it is not yet known whether these alterations have any effect on the progression of atherosclerosis. This question is being directly addressed by the STRADIVARIUS (Strategy To Reduce Atherosclerosis Development Involving Administration of Rimonabant – the Intravascular Ultrasound Study) trial [101], which will enrol obese subjects with 20 – 50% coronary artery stenosis diagnosed during clinically relevant coronary angiography. Subjects will be randomised to rimonabant or placebo and will undergo repeat angiography following 18 months of treatment, with the primary end point being change in the volume of the index atheroma (measured by intravascular ultrasound [IVUS]).

On the heels of animal experiments demonstrating that rimonabant attenuates cue reactivity and reduces drug-seeking behaviour across the wide spectrum of addictive substances, the National Institutes of Health are sponsoring a Phase II trial that will test whether therapy with rimonabant will be a useful adjunct in reducing alcohol consumption [102]. Animal experiments showing that CB1 receptor blockade with rimonabant attenuates shock due to extreme

Table 2. Clinical trials of rimonabant (as of November 2005).

Name	Status	n	Sponsor
RIO-Lipids [67]	Published	1036	Sanofi-Aventis
RIO-Europe [69]	Published	1507	Sanofi-Aventis
RIO-NA [70]	Presented	3040	Sanofi-Aventis
RIO-Diabetes [71]	Presented	1045	Sanofi-Aventis
STRATUS-US [72]	Presented	787	Sanofi-Aventis
STRATUS-EU	Enrolling	> 700 (projected)	Sanofi-Aventis
STRATUS-WW	Enrolling	> 700 (projected)	Sanofi-Aventis
STRADIVARIUS [101]	Enrolling	800 (projected)	Sanofi-Aventis
Rimonabant to reduce alcohol consumption [102]	Enrolling	40 (projected)	National Institutes of Health

NA: North American; RIO: Rimonabant in Obesity; STRADIVARIUS: Strategy To Reduce Atherosclerosis Development Involving Administration of Rimonabant – the Intravascular Ultrasound Study; STRATUS: Studies with Rimonabant And Tobacco Use; WW: Worldwide.
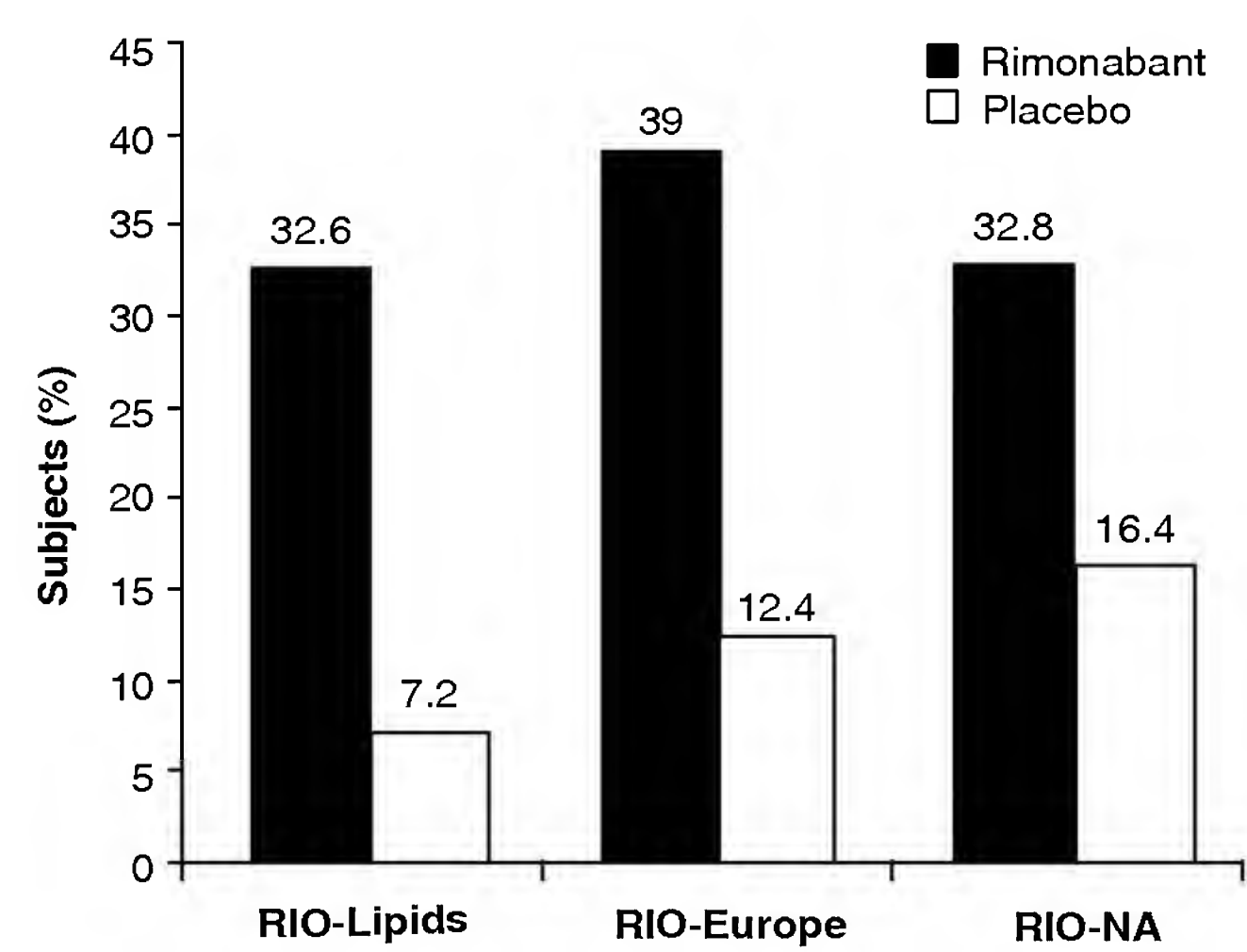

Figure 3. Percentage of subjects achieving ≥ 10% weight loss at 1 year with rimonabant 20 mg/day versus placebo in the first three RIO trials.

RIO: Rimonabant in Obesity.

haemorrhage [40], endotoxaemia [42] or myocardial infarction [41] will probably prompt human clinical trials in the near future. Rimonabant may be useful in the treatment of vasodilatory state and chronic hypotension in patients with advanced liver disease [39].

5.5 Adverse effects in clinical trials

Clinical experience with rimonabant within the scope of Phase III clinical trials involves ~ 7500 patients up-to-date and is rapidly growing. It suggests that the drug is generally well tolerated. In the RIO Phase III programme, the 1-year drop-out rates were consistently in the 36 – 49% range [69-71,73] and did not differ from placebo. The most

common adverse effect was mild nausea. In RIO-Europe, diarrhoea occurred more frequently in high-dose rimonabant group than in placebo. The rates of discontinuation due to adverse effects were 9 – 15%, and there were no study deaths attributed to the medication. Because of the endocannabinoid physiology, potential for neuropsychiatric adverse effects of rimonabant exists. These effects were carefully assessed in the clinical trials. In RIO-Europe, analysis of the Hospital Anxiety and Depression scale showed that the average subscale scores for both major depression or anxiety were similar between the treatment groups [68]. In that study, six subjects (1%) in the rimonabant 20 mg/day group and one subject (0.3%) in the placebo group discontinued their study drug because of depression. In RIO-Lipids, proportion of patients exhibiting treatment-related serious adverse events was slightly higher in rimonabant 5 mg/day and rimonabant 20 mg/day groups compared with placebo (5.2, 4.0 and 2.3%, respectively) [67]. The most common adverse effects were nausea, diarrhoea, dizziness, anxiety and insomnia. An earlier study by Meltzer and colleagues [74] demonstrated the absence of antipsychotic effects of rimonabant in patients with schizophrenia [74]. Despite the small percentage of subjects exhibiting these adverse effects with rimonabant, continued surveillance will be needed to ensure safe use of this drug.

5.6 Current regulatory status

Sanofi-Aventis has filed a new drug application for rimonabant with the FDA under the trade name Acomplia™ in 2005. The FDA declined to put its consideration of rimonabant on an accelerated track but its advisory committee is expected to take up the drug at its quarterly meeting in the first half of 2006.

6. Expert opinion

Global obesity rates and cigarette consumption are increasing. Rimonabant is the first new agent in a proposed

class of cannabinoid receptor blockers, with a set of unique, broad effects on cardiovascular and endocrine organ systems. Among obese subjects enrolled in clinical trials, rimonabant 20 mg/day p.o. leads to significant weight loss, an increase in HDL, decrease in triglycerides and a reduction in the prevalence of metabolic syndrome. In obese Type 2 diabetics, rimonabant leads to an improvement in glycaemic controls. In smokers, rimonabant enhances quit rates, and prevents weight gain that is usually associated with tobacco cessation. Trials are being conducted to determine whether rimonabant reduces the progression of coronary atherosclerosis and if it is effective in alcoholism. Side effects appear to be mild at this time, and are mainly gastrointestinal and psychiatric in nature.

Rimonabant has a significant potential to expand the clinicians' choice for treating patients with multiple cardiometabolic risk factors. As with any drug that is designed to treat a modifiable risk factor, the primary tool in this armamentarium should be intensive lifestyle modification, including a hypocaloric diet and regular exercise.

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